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Autoimmune Hepatitis: Epidemiological and Therapeutic Aspects

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Abstract: Autoimmune hepatitis (AIH) is a heterogeneous group of diseases of unknown cause, characterized by necro-inflammatory hepatocellular lesions, the presence of specific autoantibodies, and high sensitivity to corticosteroids [1]. The clinical presentation of AIH is heterogeneous; nearly one-third of patients are asymptomatic, and in 25% of cases, cirrhosis is present at diagnosis [5]. Clinical manifestations can range from mild or severe symptoms to fulminant liver failure [6], with up to 40% of patients presenting with acute hepatitis [7].

The aim of our study is to describe its epidemiological and therapeutic aspects.

Keywords: Autoimmune Hepatitis, cytolysis, corticosteroid therapy.

INTRODUCTION

Autoimmune hepatitis (AIH) is a heterogeneous group of diseases of unknown cause, characterized by necro-inflammatory hepatocellular lesions, the presence of specific autoantibodies, and high sensitivity to corticosteroids [1]. The aim of our study is to describe its epidemiological and therapeutic aspects.

MATERIALS AND METHODS

This is a descriptive retrospective study conducted within the Hepato-Gastroenterology and Proctology Department "Medicine B" over a period of 3 years. We included 16 patients.

a) Inclusion Criteria

We included all patients followed for autoimmune hepatitis based on biological and histological data.

b) Exclusion Criteria
We excluded patients with an uncertain diagnosis.

c) Data Collection
All data were collected from patient records, including:

- **Anamnestic Data:** Age, sex, place of residence, type of health coverage, medical history, and circumstances of discovery.
- **Biological Data:** Liver function tests, viral serology, liver biopsy, autoimmune workup including ANA, AMA, and IgG levels.

RESULTS

1) Demographic Data
The average age of our patients was 42.4 years, with an age range between 28 and 58 years. A female predominance was observed with a sex ratio (F/M) of 3.5. Twelve patients (75%) were from urban areas. Fourteen patients (87.5%) had health coverage.

2) Medical History
Personal history of autoimmune diseases was found in 1 patient (Autoimmune Thyroiditis).

3) Circumstances of Discovery
Autoimmune hepatitis was discovered following an acute hepatitis presentation in 4 patients (25%). Cutaneous and mucosal jaundice was present in 7 patients (43.7%). The incidental finding of hepatomegaly or liver function test abnormalities occurred in 5 patients (32.2%). Hepatic cytolysis was found in 8 patients (50%) and cholestasis in 5 patients (31%). Four patients (25%) were at the cirrhosis stage at the time of diagnosis.

4) Diagnostic Criteria
The diagnosis was made using the simplified 2008 IAIHG Score:

Table 1: IAIHG Score 2008 [2].

Variable	Seuil	Points
AAN ou AML	≥ 1/40	1
AAN ou AML	≥ 1/80	2[a]
Ou anti-LKM	≥ 1/40	
Ou anti-SLA	Positif	
IgG	> N	1
	> 1,1 N	2
Histologie hépatique (nécessité de la présence d'une hépatite)	Compatible avec une HAI	1
	Typique d'HAI	2
Absence d'hépatite virale	Oui	2
		≥ 6 : AIH probable
		≥ 7 : AIH certaine

AAN: anticorps anti-nucléaires; AML: anticorps antimuscle lisse; LKM: liver-kidney microsome; SLA: soluble liver antigen; HAI: hépatite auto-immune.
[a]*Addition des points pour tous les auto-anticorps: maximum 2 points*

5) Types of Autoimmune Hepatitis
Type 1 autoimmune hepatitis was found in 12 patients (75%), followed by type 3 autoimmune hepatitis in 4 patients (25%). An Overlap Syndrome was present in 3 patients (18.7%).

6) Treatment
Treatment was indicated in 13 patients (84%). Initial treatment was based on corticosteroids alone at a dose of 1 mg/kg/day, followed by maintenance therapy combining tapering low-dose corticosteroids and Azathioprine at a dose of 1 to 2 mg/kg/day. Corticosteroid therapy in the maintenance phase was discontinued in 10 patients. Ursodeoxycholic acid treatment at a dose of 13

to 15 mg/kg/day was indicated for patients with Overlap Syndrome. All our patients are still on maintenance therapy.

7) Evolution

The evolution was marked by the development of cirrhosis in 3 patients (18.7%). Liver function tests normalized in 12 patients (75%). Clinical and biological remission was achieved in 3 patients (18.75%). One patient died from acute fulminant hepatitis.

DISCUSSION

The incidence is 0.8 to 3 cases per 100,000 inhabitants, and the prevalence is 11 to 24 cases per 100,000 inhabitants in Europe. It currently represents about 11 to 20% of chronic hepatitis cases in Europe and America [3]. A clear female predominance is noted with a sex ratio of about 1:3, with a median age of 40 years in men and 50 years in women [4]. This aligns with our results, with a sex ratio (F/M) of 3.5 and an average age of 42.4.

The clinical presentation of AIH is heterogeneous; nearly one-third of patients are asymptomatic, and in 25% of cases, cirrhosis is present at diagnosis [5]. Clinical manifestations can range from mild or severe symptoms to fulminant liver failure [6], with up to 40% of patients presenting with acute hepatitis [7]. Fulminant or sub-fulminant presentations are estimated to occur in about 5% of cases [8]. However, isolated increases in liver enzymes and non-specific symptoms, such as arthralgia or fatigue, may be observed [9]. These findings are consistent with our study: acute hepatitis in 25% of cases, incidental findings of hepatomegaly or liver function test abnormalities in 32.2% of cases, and 25% of patients were at the cirrhosis stage at diagnosis.

In 15 to 50% of cases, extrahepatic autoimmune manifestations are associated, such as thyroid disorders, ulcerative colitis, arthritis, and dry syndrome [1]. In our study, autoimmune thyroiditis was found in 1 patient.

Biological disturbances are characterized by increased transaminase activity; however, bilirubin and alkaline phosphatase are usually normal or slightly elevated. If not, a differential diagnosis with Primary Biliary Cholangitis (PBC) or Primary Sclerosing Cholangitis (PSC) should be considered. A more specific indicator is the increase in serum gamma-globulins, particularly IgG. The essential biological marker remains the presence of autoantibodies, primarily ANA and AMA, although they can be inconsistent [10].

In our study: transaminases were elevated in 50% of cases, bilirubin in 43.7% of cases, and IgG and antibodies were present in all our patients.

Liver biopsy is characterized by necro-inflammatory lesions with a predominant periportal pattern, often marked by "piece-meal necrosis". This necrosis may be bridging or panlobular [13]. It assesses the degree of fibrosis and helps to rule out other causes or, conversely, to suggest the existence of another liver disease.

The diagnostic approach relies on excluding differential diagnoses (Hepatitis B, Steatohepatitis, PBC, PSC, Hepatitis A, Drug-Induced Hepatitis...) and on a diagnostic score proposed by the IAIHG (International Autoimmune Hepatitis Group) in 1993 [11] and a new score in 2008 [2]. Its advantage lies in its simplicity, making it more suitable for screening by practitioners.

The classification of AIH is primarily used to differentiate serological groups during clinical investigations or for prognosis. Type 1 represents about 75% of AIH cases, characterized by the presence of ANA (anti-nuclear antibodies) and especially AMA (anti-mitochondrial antibodies). Type 2 more frequently affects young women. The specific autoantibodies are directed against anti-LKM-1 (liver kidney microsome type 1) [12]. Type 3 is characterized by the presence of anti-SLA (soluble liver antigen) antibodies. In fact, the distinction of this type of AIH is debated as it appears very similar to type 1. The main interest in detecting anti-SLA antibodies is to aid in the diagnosis of patients who are seronegative for other autoantibodies, as they are found in 20% of "cryptogenic" hepatitis cases, which can be reclassified as AIH [14]. An overlap syndrome with PBC (Primary Biliary Cholangitis) or

PSC (Primary Sclerosing Cholangitis)/AIH may be observed. These findings align with our study: Type 1 was present in 75% of patients, Type 3 in 25%, and an overlap syndrome in 18.7% of patients.

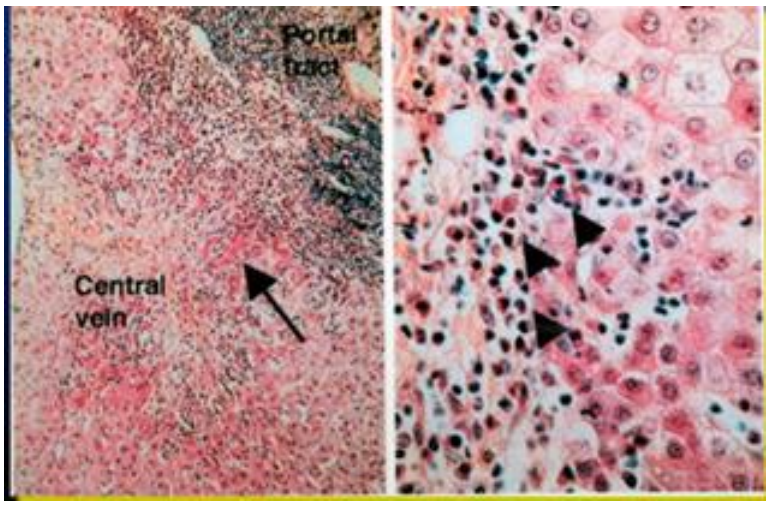

Figure: Necro-inflammatory Lesions, "Piece-meal Necrosis"

In terms of therapy, there have been no major advances in over 30 years, except for liver transplantation, which is the non-specific treatment of choice for severe forms of AIH [1]. Treatment indications according to AASLD (American Association for the Study of Liver Diseases) recommendations are as follows:

Table 2: Treatment Indications (AASLD Recommendations) [9]

Indications absolues	Indications admises
Transaminases ≥ 10 N	Symptômes (asthénie, arthralgies, ictère)
Transaminases ≥ 5 N et	Transaminases et/ou -globulines
-globulines ≥ 2 N	élevées mais inférieures aux
	critères absolus
Nécrose en pont ou	Nécrose parcellaire périportale
multilobulaire	

The standard treatment should initially include an induction phase aimed at achieving clinical and biochemical remission as quickly as possible, followed by a maintenance phase aimed at preventing subsequent flare-ups while minimizing the risk of corticosteroid-related side effects [1]. Initially, it must necessarily include a first-generation corticosteroid, with or without the addition of azathioprine. The therapeutic recommendations of the AASLD are outlined in Table 3.

Table 3: Guidelines for Initiating Standard Treatment in Adults (Adapted from AASLD Recommendations) [9]

	Prednisone seule (mg/j)	**Traitement combiné**	
		Prednisone (mg/j)	**Azathioprine (mg/j)**
Semaine 1	60	30	50
Semaine 2	40	20	50
Semaine 3	30	15	50
Semaine 4	30	15	50
Semaine 5	20	10	50
Entretien	5–20	0–10	50–100

The addition of azathioprine (50 mg/day) allows the initiation of corticosteroids at a lower dose while maintaining the same efficacy as full-dose monotherapy and reducing its side effects from 40% to 10% [15]. For patients who respond to the induction treatment, the goal is to taper corticosteroids in successive steps before discontinuing them completely. Azathioprine dosage is increased in parallel to 2 mg/kg per day. Discontinuation of corticosteroids is often achievable within the first 12 months.

In our study, all patients received induction therapy followed by maintenance therapy, and corticosteroids could be discontinued in 10 patients (77%).

Alternative therapies such as second-generation corticosteroids, calcineurin inhibitors, and anti-metabolites have not been validated in controlled trials. Therefore, they should only be considered in cases of true resistance, incomplete response, or intolerance to conventional treatment [1]. However, the efficacy of liver transplantation in cases of severe refractory or complicated AIH is well established.

Remission is defined according to AASLD criteria as the absence of symptoms, normal levels of bilirubin and gamma-globulins, transaminases less than twice the normal limit (2N), and normal or minimally inflammatory liver histology [9]. In cases of cirrhosis, it must be histologically inactive. Patients who achieve remission generally have a good prognosis. Their long-term survival is similar to that of an age- and sex-matched control population [16]. In our study, remission was achieved in 18.75% of patients.

For patients with an associated overlap syndrome, EASL recommendations suggest combining ursodeoxycholic acid (at a dose of 13 to 15 mg/kg/day) with immunosuppressive therapy [17].

Complications of AIH are similar to those observed in other liver diseases. In rare cases, AIH can present with hepatic encephalopathy [18,19]. Hepatic fibrosis is often present at diagnosis, and a subgroup of patients already has cirrhosis at presentation [20,21]. In our study, 25% of patients already had cirrhosis.
In the absence of treatment, it is estimated that 40% of patients die within 6 months of diagnosis [22]. Without adequate treatment, AIH may progress to cirrhosis and eventually to hepatocellular carcinoma, which occurs in 1% to 9% of patients with AIH [42-43]. Imaging with ultrasound or computed tomography should be performed every 6-12 months. The presence of cirrhosis at diagnosis or during treatment and the need for long-term immunosuppressive therapy have been observed as risk factors for malignant transformation [23]. In our series, cirrhosis developed in 18.7% of patients.

CONCLUSION

Autoimmune hepatitis is a rare disease with an unclear etiology and pathogenesis. Although treatment has not advanced significantly in recent years, recent diagnostic advancements have facilitated the detection of this disease. Future randomized studies with new immunosuppressive and biological treatments should improve patient management, particularly in cases of resistance, contraindication, or intolerance to corticosteroids or azathioprine.

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Informed Consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions:

All authors have contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

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